

AMENDMENTS TO THE CLAIMS

1. (Currently Amended) A liquid pharmaceutical formulation for the prolonged release of active principle(s) (AP), wherein:

- said formulation is liquid under injection conditions;

- said formulation is liquid at physiological temperature and at physiological pH and in the presence of:
a physiological electrolyte in a physiological concentration, or
at least one surfactant,

- said formulation comprises ~~comprising~~ an aqueous colloidal suspension of low viscosity based on submicronic particles of water-soluble biodegradable polymer [PO] non-covalently associated with at least one active principle (AP);
wherein said [PO] is a polyamino acid formed of aspartic residues, glutamic residues, or both aspartic and glutamic residues, at least one of said residues carrying at least one tocopherol group hydrophobic groups [HG] attached laterally to the chain, and said submicronic particles being non-covalently associated with at least one active principle (AP), wherein:
the dispersion medium of the suspension comprises water;

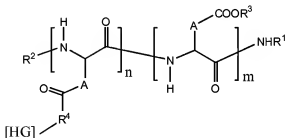
wherein the concentration of [PO] is ~~such that~~ [PO] is greater than or equal to $[\geq] 0.9.C1$, where C1 is the "induced gelling" concentration of the particles of [PO], as measured in an induced gelling (IG) test, said test comprising the following steps:

- dissolving increasing amounts of amphiphilic polymer [PO] in a dry powdered form in deionized water, and keeping the obtained solutions at 25°C for 16 hours, with magnetic stirring,
- mixing said solutions with a concentrated solution of active principle(s) to get the desired active principle(s) concentration(s)
- mixing said solutions with a concentrated aqueous solution of bovine serum albumin (BSA) containing 30 mg/ml, and centrifuging for 15 minutes at 3000 rpm,
- stirring gently for 24 h,
- measuring the relaxation time T_r of the polymer [PO] solutions to define the concentration C1 at which this time T_r exceeds 1 second; and

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- ~~said formulation prolongs and controls~~ making it possible to prolong and control the *in vivo* release time of the AP beyond 24 h after administration;
~~said formulation is liquid under the injection conditions;~~
~~and said formulation is liquid at the physiological temperature and at the physiological pH and in the presence of:~~
~~a physiological electrolyte in a physiological concentration;~~
~~or at least one surfactant.~~

2. (Canceled)
3. (Canceled)
4. (Previously Presented) The formulation according to claim 1, wherein the concentration of [PO] is: $20.C1 \geq [PO] \geq C1$.
5. (Previously Presented) The formulation according to claim 1 wherein said formulation has a viscosity less than or equal to 5 Pa.s.
6. (Canceled)
7. (Currently Amended) The formulation according to ~~claim 1~~ claim 6, the [PO] is defined by general formula (I) below:



in which:

R¹ is selected from the group consisting of: H, a linear C2 to C10 alkyl or branched C3 to C10 alkyl, benzyl, a terminal amino acid residue, and -R⁴-[HG];

R^2 is selected from the group consisting of: H, a linear C2 to C10 acyl or branched C3 to C10 acyl group, a pyroglutamate and $-R^4-[HG]$;

R^3 is selected from the group consisting of: H and a cationic entity selected from the group consisting of:

metal cations selected from the subgroup consisting of sodium, potassium, calcium and magnesium,
organic cations selected from the subgroup consisting of:
cations based on amine,
cations based on oligoamine,
cations based on polyamine, and
cations based on amino acid(s) selected from the class consisting of:
cations based on lysine or arginine,
and cationic polyamino acids selected from the subgroup comprising polylysine and oligolysine;

R^4 is a direct bond or a spacer based on 1 to 4 amino acid residues;

A independently is a radical $-CH_2-$ or $-CH_2-CH_2-$;

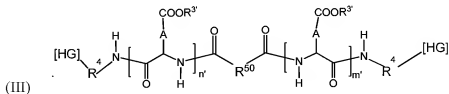
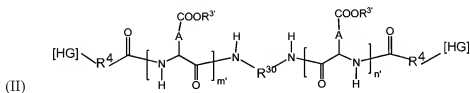
$n/(n+m)$ is defined as the molar grafting rate;

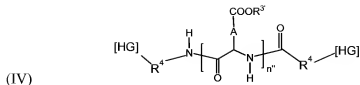
$n/(n+m)$ is between 1 and 25 mol%;

$n+m$ varies from 10 to 1000; and

[HG] is a ~~hydrophobic group~~ tocopherol.

8. (Withdrawn - Currently Amended) The formulation according to claim 1 ~~claim 6~~, the [PO] has one of general formulac (II), (III) and (IV) below:





in which:

[HG] is a hydrophobic group tocopherol;

R³⁰ is a linear C2 to C6 alkyl group;

R³ is H or a cationic entity selected from the group comprising:

metal cations selected from the subgroup consisting of sodium, potassium, calcium and magnesium,

organic cations selected from the subgroup consisting of: cations based on amine, cations based on oligoamine, cations based on polyamine, and cations based on amino acid(s) selected from the class comprising cations based on lysine or arginine, and cationic polyamino acids selected from the subgroup comprising polylysine and oligolysine;

R³⁰ is a C2 to C6 alkyl, dialkoxy or diamine group;

R⁴ is a direct bond or a "spacer" based on 1 to 4 amino acid residues;

A independently is a radical -CH₂- or -CH₂-CH₂-;

n' + m' or n'' is defined as the degree of polymerization and varies from 10 to

1000.

9. (Canceled)

10. (Canceled)

11. (Canceled)

12. (Currently Amended) The formulation according to claim 1 ~~claim-6~~, the [PO] comprises an alpha-L-glutamate or alpha-L-glutamic homopolymer.

13. (Currently Amended) The formulation according to claim 1 ~~claim 6~~, wherein the [PO] comprises an alpha-L-aspartate or alpha-L-aspartic homopolymer.

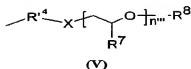
14. (Currently Amended) The formulation according to claim 1 ~~claim 6~~, wherein the [PO] comprises an alpha-L-aspartate/alpha-L-glutamate or alpha-L-aspartic/alpha-L-glutamic copolymer.

15. (Currently Amended) The formulation according to claim 14, wherein, in the [PO], the distribution of the aspartic and glutamic residues carrying grafts containing at least one tocopherol ~~[HG] residue is such that the resulting polymer~~ is either random or of the block type or of the multiblock type.

16. (Previously Presented) The formulation according to claim 1, wherein the molecular weight of the [PO] is between 2,000 and 100,000 g/mol.

17. (Currently Amended) The formulation according to claim 1 ~~claim 6~~, wherein the [PO] further carries at least one graft of polyalkylene glycol type bonded to a glutamate or an aspartate residue.

18. (Previously Presented) The formulation according to claim 17, wherein the graft of polyalkylene glycol type has formula (V) below:



in which:

R⁴ is a direct bond or a "spacer" based on 1 to 4 amino acid residues;

X is a heteroatom selected from the group consisting of: oxygen, nitrogen and sulfur;

R⁷ and R⁸ independently are H or a linear C1 to C4 alkyl;

n''' varies from 10 to 1000.

19. (Previously Presented) The formulation according to claim 17, wherein the polyalkylene glycol is a polyethylene glycol.

20. (Previously Presented) The formulation according to claim 17, wherein the molar percentage of polyalkylene glycol grafting varies from 1 to 30%.

21. (Canceled)

22. (Previously Presented) The formulation according to claim 1, wherein the AP is selected from the group consisting of: a protein, a glycoprotein, a protein bonded to one or more polyalkylene glycol chains, a polysaccharide, a liposaccharide, an oligonucleotide, a polynucleotide and a peptide.

23. (Previously Presented) The formulation according to claim 1, wherein the AP is a "small" hydrophobic, hydrophilic or amphiphilic organic molecule.

24. (Currently Amended) The formulation according to claim 1, wherein the weight fraction of AP not associated with the submicronic particles [non-associated AP], in weight %, is ≤ 1 .
~~such that~~ [non-associated AP] ≤ 1 .

25. (Previously Presented) The formulation according to claim 1 wherein the formulation is injectable by the parenteral, subcutaneous, intramuscular, intradermal, intraperitoneal or intracerebral route or into a tumour.

26. (Previously Presented) The formulation according to claim 1 wherein the formulation is used to prepare drugs for administration by the parenteral, subcutaneous, intramuscular, intradermal, intraperitoneal or intracerebral route or into a tumour, or by the oral, nasal, vaginal or ocular route.

27. (Withdrawn) Process for the preparation of drugs, particularly for administration by the parenteral, subcutaneous, intramuscular, intradermal, intraperitoneal or intracerebral route

or into a tumour, or by the oral, nasal, vaginal or ocular route comprising at least one formulation according to claim 1.

28. (Previously Presented) A derived product comprising submicronic particles formed of non-covalent PO/AP associations as defined in claim 1, and obtained from the formulation according to claim 1.

29. (Previously Presented) The derived product according to claim 28, said product is in a powder or a gel form.

30. (Withdrawn) A process for the preparation of the formulation of claim 1, said process comprising the steps of:
taking a colloidal suspension of nanoparticles of at least one PO,
mixing this colloidal suspension of nanoparticles of PO with at least one AP, in aqueous solution, and
adjusting the pH and/or the osmolarity if necessary.

31. (Withdrawn) A process according to claim 30, wherein the at least one AP is in the form of an aqueous suspension or solution for mixing with the colloidal suspension of nanoparticles of PO.

32. (Withdrawn) A process for the preparation of the formulation of claim 1, said process comprising the steps of:
taking a powder of nanoparticles of at least one PO,
mixing this powder with an aqueous suspension or solution of at least one AP, in aqueous solution, and
adjusting the pH and/or the osmolarity if necessary.

33. (Withdrawn) A process for the preparation of the formulation of claim 1, said process comprising the steps of:
taking a powder produced by drying the liquid formulation according to claim 1,
mixing this powder with an aqueous liquid medium, and

adjusting the pH and/or the osmolarity if necessary.

34. (Withdrawn) A process for the preparation of a powder derived from the formulation of claim 1, wherein said powder is obtained by drying the formulation of claim 1.

35. (Previously Presented) The formulation according to claim 1, wherein the concentration of [PO] is: $10.C1 \geq [PO] \geq C1$.

36. (Previously Presented) The formulation according to claim 1, wherein the molecular weight of the [PO] is between 5,000 and 40,000 g/mol.